

What is claimed is:

1. A polyamide suitable for inhibiting the transcription of a gene, the polyamide comprising:

5 at least three complementary pairs of aromatic carboxamide residues, the complementary pairs of aromatic carboxamide residues being selected to correspond to a nucleotide sequence of an identified dsDNA target;

at least two aliphatic amino acid residues chosen from the group consisting of glycine, β -alanine, γ -aminobutyric acid, R 2,4-diaminobutyric acid, and 5-aminovaleric
10 acid; and

at least one terminal alkylamino residue.

2. The polyamide of claim 1 wherein the complementary pairs of aromatic carboxamide residues selected to correspond to the nucleotide sequence of the
15 identified dsDNA target are chosen from the group consisting of

Im/Py to correspond to the nucleotide pair G/C,

Py/Im to correspond to the nucleotide pair C/G,

Py/Py to correspond to the nucleotide pair A/T,

Py/Py to correspond to the nucleotide pair T/A,

20 Hp/Py to correspond to the nucleotide pair T/A, and

Py/Hp to correspond to the nucleotide pair A/T,

where Im is N-methyl imidazole, Py is N-methyl pyrrole, and Hp is 3-hydroxy N-methyl pyrrole.

25 3. The polyamide of claim 1 wherein the nucleotide sequence of the identified dsDNA target is chosen from the group consisting of

5'-TGCTTGA-3',

5'-AGAATGA-3',

5'-TGAGGAA-3',

5'-TGCTTGA-3',
 5'-TGAGGAA-3',
 5'-AGGAAGT-3',
 5'-ATGAAGT-3',
 5'-AGTATAA-3',
 5'-AGTATAA-3',
 5'-AGGAAGT-3',
 5'-AGTATAA-3',
 5'-AGTATAA-3',
 5'-AACGGCT-3',
 5'-TGCAGGCA-3',
 5'-AACGGCT-3',
 5'-TGCAGGCA-3', and
 5'-AGGCAA-3'.

4. The polyamide of claim 1 wherein the transcription of the gene is inhibited by modulating the binding to dsDNA of a protein factor chosen from the group consisting of ESX, ETS, AP-2, and TBP.
5. The polyamide of claim 1 wherein at least one aliphatic amino acid residue is β -alanine.
6. The polyamide of claim 1 wherein the terminal alkylamino residue is a N,N-dimethylaminopropyl residue.
7. The polyamide of claim 5 wherein two β -alanine residues form complementary paired residues corresponding to a nucleotide pair chosen from the group A/T and T/A.

8. The polyamide of claim 1 wherein one aliphatic amino acid residue is R 2,4-diaminobutyric acid.
- 5 9. The polyamide of claim 1 having a binding affinity for the target dsDNA sequence of at least 10^9 M^{-1} and a selectivity of at least about two, selectivity being defined as the ratio of the binding affinity for the identified target dsDNA sequence to the binding affinity for a single base-pair mismatch dsDNA sequence.
- 10 10. A polyamide suitable for inhibiting the transcription of an oncogene, the polyamide comprising:
- at least three complementary pairs of aromatic carboxamide residues, the complementary pairs of aromatic carboxamide residues being selected to correspond to a nucleotide sequence of an identified dsDNA target, at least two aliphatic amino acid
- 15 residues chosen from the group consisting of glycine, β -alanine, γ -aminobutyric acid, R 2,4-diaminobutyric acid, and 5-aminovaleric acid, and at least one terminal alkylamino residue, the polyamide having a binding affinity at the target dsDNA sequence of at least 10^9 M^{-1} and a selectivity of at least about two, selectivity being defined as the ratio of the binding affinity for the nucleotide sequence of the identified dsDNA target to the binding
- 20 affinity for a single base-pair mismatch sequence dsDNA.
11. The polyamide of claim 10 wherein the complementary pairs of aromatic carboxamide residues selected to correspond to the nucleotide sequence of an identified dsDNA target are chosen from the group consisting of
- 25 Im/Py to correspond to the nucleotide pair G/C,
Py/Im to correspond to the nucleotide pair C/G,
Py/Py to correspond to the nucleotide pair A/T,
Py/Py to correspond to the nucleotide pair T/A,

Hp/Py to correspond to the nucleotide pair T/A, and
Py/Hp to correspond to the nucleotide pair A/T,
where Im is N-methyl imidazole, Py is N-methyl pyrrole and Hp is 3-hydroxy N-methyl pyrrole.

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12. The polyamide of claim 10 wherein the nucleotide sequence of the identified dsDNA target is chosen from the group consisting of
- 5'-TGCTTGA-3',
5'-AGAATGA-3',
10 5'-TGAGGAA-3',
5'-TGCTTGA-3',
5'-TGAGGAA-3',
5'-AGGAAGT-3',
5'-ATGAAGT-3',
15 5'-AGTATAA-3',
5'-AGTATAA-3',
5'-AGGAAGT-3',
5'-AGTATAA-3',
5'-AGTATAA-3',
20 5'-AACGGCT-3',
5'-TGCAGGCA-3',
5'-AACGGCT-3',
5'-TGCAGGCA-3', and
5'-AGGCAA-3'.
- 25
13. The polyamide of claim 10 wherein the transcription of the gene is inhibited by modulating the binding to dsDNA of a protein factor chosen from the group consisting of ESX, ETS, AP-2, and TBP.

14. The polyamide of claim 10 wherein at least one aliphatic amino acid residue is β -alanine.
- 5 15. The polyamide of claim 14 wherein two β -alanine residues form complementary — paired residues corresponding to a nucleotide pair chosen from the group A/T and T/A.
16. The polyamide of claim 10 wherein one aliphatic amino acid residue is R 2,4-
10 diaminobutyric acid.
17. The polyamide of claim 10 wherein the terminal alkylamino residue is a N,N-dimethylaminopropyl residue.
- 15 18. The polyamide of claim 10 wherein at least one Py of a carboxamide pair is replaced by a β -alanine.
19. A composition comprising a pharmaceutically acceptable excipient and a transcription-inhibiting amount of at least one polyamide, each polyamide
20 comprising:
at least three complementary pairs of aromatic carboxamide residues, the complementary pairs of aromatic carboxamide residues being selected to correspond to a nucleotide sequence of an identified dsDNA target; and
at least two aliphatic amino acid residues chosen from the group consisting of
25 glycine, β -alanine, γ -aminobutyric acid, R 2,4-diaminobutyric acid, and 5-aminovaleric acid, and at least one terminal alkylamino residue, the polyamide having a binding affinity at the target dsDNA sequence of at least 10^9 M^{-1} and a selectivity of at least about two, selectivity being defined as the ratio of the binding affinity for the identified target

dsDNA sequence to the binding affinity for a single base-pair mismatch dsDNA sequence.

20. The composition of claim 19 wherein the complementary pairs of aromatic
5 carboxamide residues selected to correspond to the nucleotide sequence of the identified dsDNA target are chosen from the group consisting of

Im/Py to correspond to the nucleotide pair G/C,

Py/Im to correspond to the nucleotide pair C/G,

Py/Py to correspond to the nucleotide pair A/T,

10 Py/Py to correspond to the nucleotide pair T/A,

Hp/Py to correspond to the nucleotide pair T/A, and

Py/Hp to correspond to the nucleotide pair A/T,

where Im is N-methyl imidazole, Py is N-methyl pyrrole, and Hp is 3-hydroxy N-methyl pyrrole.

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21. The composition of claim 19 wherein the nucleotide sequence of the identified dsDNA target is chosen from the group consisting of

5'-TGCTTGA-3',

5'-AGAATGA-3',

20 5'-TGAGGAA-3',

5'-TGCTTGA-3',

5'-TGAGGAA-3',

5'-AGGAAGT-3',

5'-ATGAAGT-3',

25 5'-AGTATAA-3',

5'-AGTATAA-3',

5'-AGGAAGT-3',

5'-AGTATAA-3',

5'-AGTATAA-3',
5'-AACGGCT-3',
5'-TGCAGGCA-3',
5'-AACGGCT-3',
5'-TGCAGGCA-3', and
5'-AGGCAA-3'.

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22. The composition of claim 19 wherein at least one aliphatic amino acid residue is β -alanine.

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23. The composition of claim 19 wherein the terminal alkylamino residue is a N,N-dimethylaminopropyl residue.

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24. The composition of claim 23 wherein two β -alanine residues form complementary paired residues corresponding to a nucleotide pair chosen from the group A/T and T/A.

25. The composition of claim 19 wherein one aliphatic amino acid residue is R 2,4-diaminobutyric acid.

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